Association between apolipoprotein E4 and cognitive decline in elderly adults

Association Between Apolipoprotein E_4 and Cognitive Decline in Elderly Adults

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OBJECTIVE: To determine the influence of apolipoprotein E on cognitive decline in a cohort of elderly men and women.

DESIGN: Prospective study.

SETTING: Scotland, Ireland, and the Netherlands.

PARTICIPANTS: Five thousand eight hundred four subjects aged 70 to 82 from the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER).

MEASUREMENTS: Subjects were assessed at baseline and over a mean 3.2-year (range 0.7–4.2) follow-up for memory (Picture-Word Recall), speed of information processing (Stroop and Letter-Digit Coding), global cognitive function (Mini-Mental State Examination), and activities of daily living.

RESULTS: At baseline, subjects with apolipoprotein E_4 versus those without E_4 had poorer memory performance (mean score difference -0.20 (95% confidence interval (CI) = -0.31 to -0.09) for immediate recall and -0.32 (95% CI = -0.48 to -0.16) for delayed recall and slower information processing (difference in Stroop, 2.79 seconds, (95% CI = 1.20–4.28); Letter-Digit score, -0.36, (95% CI = -0.77–0.05). Subjects with apolipoprotein E_4 showed a greater decline in immediate (-0.22, 95% CI = -0.33 to -0.11) and delayed (-0.30, 95% CI = -0.46 to -0.15) memory scores but no significant change in speed of information processing (Stroop, $P = .17$; Letter-Digit, $P = .06$). Memory scores decreased 2.5% from baseline in those without E_4, 4.3% in E_4 heterozygotes ($P = .01$ for immediate and $P = .03$ for delayed, vs no E_4) and 8.9% to 13.8% in E_4 homozygotes ($P = .04$ for immediate and $P = .004$ for delayed, vs heterozygotes). Apolipoprotein E_4 was associated with greater decline in instrumental activities of daily living ($P < .001$). Cognitive decline was not associated with lipoprotein levels.

CONCLUSION: Findings in PROSPER indicate that E_4 is associated with more-rapid cognitive decline and may, therefore, predispose to dementia. **J Am Geriatr Soc 55:1777–1785, 2007.**

Key words: memory; dementia; trial; statin

A major challenge in the quest to promote healthy aging is to uncover the determinants of cognitive decline in the general population and the risk factors that lead to the development of frank dementia. Although age is the main predictor of cognitive function, investigators have also reported that a history of hypertension, diabetes mellitus, stroke, depression, and lack of physical activity are factors.[1–6] The apolipoprotein E phenotype (apolipoprotein E is coded by a gene (ε) that exhibits allelic variants ε_2, ε_3, and ε_4) has been linked consistently and strongly to the appearance of Alzheimer's disease and to some aspects of cognitive decline in elderly cohorts.[1,2,5–9] Inheritance of E_4 (the product of ε_4) especially in the homozygous form, has been associated in cross-sectional studies with risk of Alzheimer's disease and poorer global cognitive function, episodic memory, and executive function, although the magnitude of the effect is modest.[10,11] Longitudinal data also show good evidence of an association between E_4 and risk of Alzheimer's disease and dementia,[12,13] although the rela-

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tionship between the E_4 genotype and age-associated cognitive decline without dementia has been less clear.[14] One study[15] found a link in twins between E_4 and deterioration of working memory, and others have reported greater decline in verbal memory and executive function in those with E_4.[16–18] In contrast, another study[13] found that possession of E_4 did not modify progression of cognitive decline in the preclinical period of Alzheimer's disease, and a third study[19] reported slower rates of memory decline in E_4 carriers. Likewise, it was found that E_4 did not contribute to prediction of cognitive decline in the very old but that cerebrovascular disease was a major risk factor for this and for progression to dementia.[20] It is important, therefore, to widen the evidence base for the effects of E_4 on cognitive decline before the appearance of dementia to assess how early this genetic variation has an effect. The role of apolipoprotein E in brain physiology and the precise nature of the influence of the phenotypic variation on the pathogenesis of neurodegenerative disease is unknown, although clues are emerging from molecular studies[21] and from investigations of white matter structure.[22]

The nature of the association between lipid and lipoprotein levels and cognitive impairment is largely unknown, with conflicting results being reported.[23–26] Recently, low high-density lipoprotein cholesterol (HDL-C) levels have been linked to poorer cognitive function, independent of an effect on cardiovascular disease in the oldest old,[23] whereas no association between total plasma cholesterol or HDL-C and risk of Alzheimer's disease was observed in another study.[26]

The Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) was a trial of statin use for the prevention of cardiovascular and cerebrovascular disease in 5,804 men and women aged 70 to 82.[27] It demonstrated that pravastatin treatment was associated with a reduction in vascular events. Part of the trial design was to examine the effect of statin therapy on cognition. To this end, a battery of cognitive function tests was administered at baseline and annually during follow-up[28] and linked to initial lipid levels, apolipoprotein E phenotype, and treatment allocation. It was reported previously that pravastatin use did not affect cognitive decline.[27] Here, the effect of apolipoprotein E phenotype and lipoprotein levels on cognitive function at baseline and on cognitive decline are described in this large cohort. On the basis of previous work in smaller studies and the role of vascular disease in dementia, the working hypothesis was that apolipoprotein E phenotype and levels of low-density lipoprotein cholesterol (LDL-C) and HDL-C would influence cognition.[29–31]

METHODS

Study Design and Subjects

PROSPER was a trial of statin use in preventing coronary and cerebrovascular events in older subjects with a history of vascular disease or at high risk of an event due to a history of smoking, hypertension, or diabetes mellitus.[32] A total of 5,804 individuals (2,804 men, 3,000 women; aged 70–82) were recruited in Scotland, Ireland, and the Netherlands and randomized to receive 40 mg/d pravastatin or placebo daily. Follow-up was for 3.2 years on average (range 0.7–4.2 years). As part of the design of the study, whether statin treatment had any effect on cognitive decline was assessed by administering a battery of cognitive function tests.[28] Determinants of cognitive function at baseline and of cognitive decline were sought from the risk factor profiles, including apolipoprotein E phenotype, which was assessed during screening. There were restrictions on entry; plasma cholesterol had to be in the range of 4.0 to 9.0 mmol/L and plasma triglyceride less than 6.0 mmol/L. The institutional ethics review boards of the centers approved the study, and all participants gave written informed consent.

Measurements

Plasma cholesterol, triglyceride, LDL-C, and HDL-C were measured twice at fasting visits during the placebo run-in phase according to the Lipid Research Clinics protocol[33] in a central laboratory that was standardized through the Centers for Disease Control and Prevention network. Apolipoprotein E phenotype was determined on plasma samples using Western blotting following a method previously established.[34] Subjects were classified according to the presence of the E_2, E_3, or E_4 bands on gel blots. The gel phenotyping method shows high concordance (>95%) with genotype testing according to allele-specific oligonucleotide assay (unpublished results).

A detailed description of the cognitive tests used in the study has been published previously.[28] The Mini-Mental State Examination (MMSE) is used widely to screen for cognitive impairment and dementia.[35] A cutoff score of 24 points or more (out of 30) was used as an inclusion criterion to eliminate those with poor cognitive function at baseline. Memory was tested using the Picture-Word Recall test based on the Groningen-Fifteen Words test.[28,36] This measures recall, both immediate and after 20 minutes, of 15 pictures (rather than words, to overcome any language problem). The outcome variable is the mean number of correctly recalled pictures over three immediate trials and number recalled after the delay. Attention and processing were assessed using the Stroop-Color Word test[37] and the Letter-Digit Coding test.[28] The former, in the key Part III of the test, presents color names printed in incongruously colored ink (e.g., the word green printed in blue ink). Performance, timed in seconds to complete the test, measures the ability to discard the irrelevant name (green) in favor of the color of the ink (blue). The latter asks the subject to fill in digits next to letters according to a key; the outcome is the number of correct entries in 60 seconds. Subjects were assessed twice (2 weeks apart) at baseline to allow for any training effect. The results of the second test were taken as the starting estimate of cognitive function. Decline in basic activities of daily living (ADLs) was assessed using the 20-point variation[38] of the Barthel Index[39] and in extended activities instrumental activities of daily living (IADLs) using a 14-point score.[40] All tests were repeated at 9, 18, and 30 months and at the final trial visit. Dementia was recorded as an adverse event if diagnosed by an attending physician; no trial-specific assessment was performed, and it was not an adjudicated endpoint.

Statistical Analyses

Subjects were divided initially into three categories (E_4+ (phenotypes $E_{3/4}$, $E_{2/4}$, and $E_{4/4}$), $E_{3/3}$ (the common-

est phenotype), and E_2+ (phenotypes $E_{2/3}$ and $E_{2/2}$)) to test for an effect of phenotype on cognition. No significant difference was seen in any result between $E_{3/3}$ and E_2+ subjects, and these were combined into an E_4- category. Baseline characteristics were compared between the E_4+ and E_4- groups using two-sample *t*-tests for continuous variables and the chi-square test for categorical variables. As part of this demographic assessment, overall risk of stroke was estimated as described previously,[41] and the computed risk was compared between E_4+ and E_4- subjects. Cognitive measures at baseline and decline in cognition were compared between phenotype categories using linear models adjusted for age, sex, country, educational attainment, history of vascular disease, history of myocardial infarction, history of stroke or transient ischemic attack, smoking, use of antihypertension medication, blood pressure, body mass index, history of diabetes mellitus, triglyceride and lipoprotein cholesterol levels, and where appropriate, version of test used. Models for change in cognitive function from baseline (referred to as cognitive decline) were also adjusted for treatment allocation and baseline test scores. Adjusted least square means and standard errors are reported for each of the three original phenotype categories, and mean differences with 95% confidence intervals (CIs) and *P*-values are given for the E_4+ and E_4- groups. Cognitive decline was defined as the difference between subjects' last recorded follow-up measurement and the second of two baseline measurements. In further analyses, only subjects with MMSE scores of 26 to 30 were included (n = 5,295). Time to dementia (as a recorded adverse event), or in a separate analysis to an MMSE score less than 24, in the E_4+ and E_4- groups was estimated using Cox proportional hazard models. Kaplan-Meier curves were generated for incident dementia in the E_4+ and E_4- groups.

The E_4+ group was split into E_4 homozygotes ($E_{4/4}$) and E_4 heterozygotes ($E_{2/4}$ and $E_{3/4}$). Mean results of cognition tests at baseline, and of cognitive decline, were compared between these phenotypes and the E_4- group. Results were also analyzed as percentage change over baseline. An average percentage decline in memory function was calculated from the results of the immediate and delayed Picture-Word recall. This variable was then compared in E_4-, E_4 heterozygotes, and E_4 homozygotes in subjects with baseline MMSE scores of 24 to 30 (evaluable subjects, n = 5,004), 26 to 30 (n = 4,611), and 28–30 (n = 3,456).

Repeated-measures models that included all of the measurements recorded on a subject and incorporated a linear separation between the groups were investigated, although these more-complex models did not add statistical power, possibly because of the additional assumptions made being invalid. This approach is not reported here; rather the simpler change from baseline analysis was used.

To examine the association between cognition and LDL-C and HDL-C, linear models were constructed as for apolipoprotein E analysis. For descriptive purposes, least squares means and standard errors adjusted for baseline variables, as noted previously, as well as apolipoprotein E_4 status, are given for tertiles of LDL-C and HDL-C. *P*-values for continuous measures of HDL-C and LDL-C are also reported.

For all analyses, only complete and reliable test results of cognitive function (as indicated by the study nurse who administered the test) were included.

RESULTS

Of the 5,804 subjects recruited to the study, apolipoprotein E phenotyping was available for 95.5%; 38 (0.7%) were $E_{2/2}$, 621 (11.2%) were $E_{2/3}$, 119 (2.2%) were $E_{2/4}$, 3,496 (63.1%) were $E_{3/3}$, 1,169 (21.1%) were $E_{3/4}$, and 101 (1.8%) were $E_{4/4}$. Translated into genotypes, the frequencies were in Hardy-Weinberg equilibrium. Thus, a total of 4,155 subjects were classified as E_4- and 1,389 as E_4+. In univariate analysis, the latter group had higher plasma total cholesterol (mean ± standard deviation 5.84 ± 0.91 vs 5.63 ± 0.90 mmol/L, $P < .001$), higher LDL-C (3.96 ± 0.81 vs 3.74 ± 0.79 mmol/L, $P < .001$), lower HDL-C (1.25 ± 0.34 vs 1.29 ± 0.35 mmol/L, $P < .001$), and higher plasma triglyceride (1.60 ± 0.75 vs 1.52 ± 0.68 mmol/L, $P < .001$) levels than the former. No significant difference was observed in blood pressure; sex; history of coronary disease, stroke, or hypertension; smoking habit; years of education; or a composite score of stroke risk.[41] Subjects with diabetes mellitus were approximately 25% less prevalent in the E_4+ group ($P = .007$). Subjects who were E_4+ were marginally younger than those who were E_4-.

At baseline, age, sex, and educational status were major determinants of all tests of cognitive function. History of stroke, diabetes mellitus, and smoking were predictors of scores in the Stroop and Letter-Digit Coding tests but not of memory function (i.e., immediate and delayed Picture-Word Recall). History of vascular disease, history of stroke, body mass index, diabetes mellitus, and smoking were predictors of scores in the Barthel and IADL indices (data not shown).

Influence of Apolipoprotein E Phenotype

Apolipoprotein E phenotype had a significant association with a number of tests of cognitive function, determined upon entry into the study (Table 1). As discussed in the Methods section, none of the E_2+ versus $E_{3/3}$ comparisons indicated a significant difference, and these phenotypes were combined in the E_4- category. Subjects in the E_4+ group performed significantly less well on the Stroop test and Picture-Word Recall (immediate and delayed) than subjects in the E_4- group and had marginally, but significantly, poorer scores on the MMSE (Table 1). No significant influence of apolipoprotein E_4 status was seen for the Letter-Digit Coding test or the Barthel or IADL indices. Restricting the analyses to subjects with baseline MMSE scores of 26 to 30 did not alter these associations (data not shown).

Follow-up assessments on at least one of the cognitive tests were available for 98.4% (5,454/5,544) of subjects with apolipoprotein E phenotyping available, and 4,942 completed at least 3 years of assessment. Of the 90 subjects without any follow-up assessment, 72 died, 11 refused to participate or did not attend a follow up cognitive assessment, and seven had a nonfatal adverse event. Over the average 3.2 years (range 0.7–4.2 years) of follow-up, apolipoprotein E_4 status significantly influenced change in scores on the cognitive tests associated with memory (immediate and delayed Picture-Word Recall) but not those for attention and processing (Stroop, Letter-Digit Coding) (Table 2). Again, none of the comparisons between $E_{3/3}$ and E_2+ subjects was significant. Those in the E_4+ group had significantly greater decrements than those in the E_4- group on MMSE, Barthel, and IADL scores. At the

Table 1. Comparison of Baseline Measures of Cognition According to Apolipoprotein E Phenotype

Cognitive Test and Apolipoprotein E Phenotype*	Baseline, Least Square Mean (Standard Error†)	E_4+ versus E_4 − Mean Difference (95% Confidence Interval)‡	*P*-Value‡
Stroop Part III (seconds to complete) (n = 5,163)			
E_4+	71.1 (0.93)§	2.79 (1.30, –4.28)	<.001
$E_3/_3$	68.3 (0.77)		
E_2+	68.1 (1.17)		
Letter-Digit Coding (number correct) (n = 5,185)			
E_4+	22.1 (0.26)	− 0.36 (0.77, –0.05)	.08
$E_3/_3$	22.5 (0.21)		
E_2+	22.5 (0.32)		
Picture-Word Recall (number recalled) (n = 5,222)			
Immediate			
E_4+	9.16 (0.07)§	− 0.20 (− 0.31, − 0.09)	<.001
$E_3/_3$	9.35 (0.06)		
E_{2+}	9.44 (0.09)		
Delayed			
E_4+	9.77 (0.10)§	− 0.32 (− 0.48, − 0.16)	<.001
$E_3/_3$	10.07 (0.08)		
E_2+	10.24 (0.12)		
Barthel Index (score) (n = 5,544)			
E_4+	19.6 (0.03)	− 0.04 (− 0.08, –0.00)	.08
$E_3/_3$	19.6 (0.02)		
E_2+	19.7 (0.03)		
Instrumental activity of daily living index (score) (n = 5,544)			
E_4+	13.4 (0.04)	− 0.05 (− 0.11, –0.01)	.12
$E_3/_3$	13.4 (0.03)		
E_{2+}	13.4 (0.05)		
Mini-Mental State Examination (score) (n = 5,479)			
E_4+	27.8 (0.06)§	− 0.21 (− 0.30, − 0.12)	<.001
$E_3/_3$	28.0 (0.05)		
E_2+	28.0 (0.07)		

* E_4+ includes $E_4/_4$, $E_4/_3$, and $E_4/_2$ phenotypes, E_2+ includes $E_3/_2$ and $E_2/_2$.
† Adjusted for age, sex, country, education, history of vascular disease, history of myocardial infarction, history of diabetes mellitus, history of stroke or transient ischemic attack, smoking, use of antihypertensive medication, blood pressure, body mass index, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglyceride, and where applicable test version.
‡ Comparison of mean test results in E_4+ ($E_{4/4}$, $E_{4/2}$, $E_{4/3}$) subjects versus E_4 − ($E_{3/3}$, $E_{2/3}$, $E_{2/2}$) subjects.
§ Apolipoprotein E_4+ group result was significantly different from $E_{3/3}$ and E_2+ result.

Table 2. Comparison of Change in Cognitive Function According to Apolipoprotein E Phenotype

Cognitive Test and Apolipoprotein E Phenotype*	Change, Least Square Mean (Standard Error)†	E_4+ versus E_4 − Mean Difference (95% Confidence Interval)‡	*P*-Value‡
Stroop Part III (seconds to complete) (n = 4,897)§			
E_4+	+5.99 (0.85)	+0.95 (0.39–2.29)	.17
$E_3/_3$	+5.02 (0.70)		
E_2+	+5.14 (1.06)		
Letter-Digit Coding (number correct) (n = 4,953)			
E_4+	− 1.88 (0.18)	− 0.26 (0.53–0.01)	.06
$E_3/_3$	− 1.60 (0.14)		
E_2+	− 1.77 (0.21)		
Picture Word Recall (number recalled) (n = 5,004)			
Immediate			
E_4+	− 0.52 (0.068)‖#	− 0.22 (0.33, − 0.11)	<.001
$E_3/_3$	− 0.30 (0.056)		
E_2+	− 0.31 (0.085)		
Delayed			
E_4+	− 0.82 (0.098)‖	− 0.30 (0.46, − 0.15)	<.001
$E_3/_3$	− 0.51 (0.080)		
E_2+	− 0.58 (0.121)		
Barthel Index (score) (n = 5,453)			
E_4+	− 0.63 (0.068)‖	− 0.13 (0.24, − 0.02)	.02
$E_3/_3$	− 0.51 (0.056)		
E_2+	− 0.48 (0.086)		
Instrumental activity of daily living index (score) (n = 5,454)			
E_4+	− 1.20 (0.082)‖#	− 0.32 (0.45, − 0.18)	<.001
$E_3/_3$	− 0.89 (0.068)		
E_2+	− 0.87 (0.10)		
Mini-Mental State Examination (score) (n = 5,260)			
E_4+	− 0.42 (0.072)‖#	− 0.27 (0.39, − 0.16)	<.001
$E_3/_3$	− 0.15 (0.060)		
E_2+	− 0.12 (0.091)		

* E_4+ includes $E_{4/4}$, $E_{4/3}$, $E_{4/2}$; E_2+ includes $E_{2/3}$, $E_{2/2}$.
† Change score (last recorded result minus baseline result) adjusted for age, sex, country, education, history of vascular disease, history of myocardial infarction, history of diabetes mellitus, history of stroke or transient ischemic attack, smoking, use of antihypertensive medication, blood pressure, body mass index, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglyceride, and where applicable test version, plus baseline test score and treatment allocation.
‡ Comparison of mean change in E_4+ and E_4 − groups.
§ A positive change in the Stroop test indicates deteriorating performance.
‖ Apolipoprotein E_4+ group result was significantly different from $E_{3/3}$ result.
Apolipoprotein E_4+ group result was significantly different from E_2+ result.

end of the study, 85 (6.4%) in the E_4+ group and 131 (3.3%) in the E_4 − group had scores less than 24 on the MMSE ($P<.001$ for difference in incidence), and there were 37 cases of dementia reported as an adverse event (2.7%) in the E_4+ group and 46 (1.1%) in the E_4 − group, a 2.48-fold difference in risk ($P<.001$). Including only those with MMSE scores of 26 to 30 at baseline produced the same qualitative result (data not shown).

Treatment assignment (i.e., to placebo or pravastatin therapy) was included in the multivariate models. It was reported previously that pravastatin use during the trial had no significant effect on change in cognitive function.[42] This was further tested by examining the interaction between apolipoprotein E phenotype, treatment, and cognition. No significant associations were found with any of the tests, confirming the lack of effect of statin therapy on cognitive decline (data not shown).

Gene Dose Effect

Further analyses were performed in which E_4 homozygotes were considered separately from E_4 heterozygotes (Table 3). At baseline, neither E_4 homozygotes nor E_4 heterozygotes differed from E_4 − on the Letter-Digit Coding test or on the

Table 3. Apolipoprotein E4 Status and Cognitive Function

Cognitive Test	E_4- (N = 4,155)*	E_4 Heterozygotes (N = 1,288)*	E_4 Homozygotes (N = 101)*	*P*-Value†
	Least Square Mean (Standard Error)			
Stroop Part III (seconds to complete)‡				
Baseline (n = 5,163)	68.3 (0.75)	71.1 (0.95)§	70.1 (2.52)	.001
Change (n = 4,897)	+5.04 (0.68)	+5.73 (0.86)	+9.42 (2.28)	.10
Letter-Digit Coding (number correct)				
Baseline (n = 5,185)	22.5 (0.21)	22.2 (0.26)	21.4 (0.70)	.12
Change (n = 4,953)	− 1.63 (0.14)	− 1.85 (0.17)	− 2.41 (0.46)	.08
Picture-Word Recall (number recalled)				
Immediate				
Baseline (n = 5,222)	9.36 (0.055)	9.18 (0.070)§	8.93 (0.185)§	<.001
Change (n = 5,004)	− 0.30 (0.054)	− 0.49 (0.069)§	− 1.00 (0.184)§**	<.001
Delayed				
Baseline (n = 5,222)	10.09 (0.079)	9.81 (0.100)§	9.33 (0.264)§	<.001
Change (n = 5,004)	− 0.52 (0.078)	− 0.76 (0.099)	− 1.72 (0.264)§**	<.001
Barthel Index (score)				
Baseline (n = 5,544)	19.6 (0.022)	19.6 (0.027)	19.6 (0.073)	.21
Change (n = 5,453)	− 0.51 (0.055)	− 0.63 (0.069)	− 0.72 (0.185)	.06
Instrumental activities of daily living index (score)				
Baseline (n = 5,544)	13.4 (0.030)	13.4 (0.038)	13.4 (0.101)	.30
Change (n = 5,454)	− 0.89 (0.066)	− 1.20 (0.083)§	− 1.18 (0.223)	<.001
Mini-Mental State Examination (score)				
Baseline (n = 5,479)	28.0 (0.046)	27.8 (0.058)§	27.6 (0.153)§	<.001
Change (n = 5,260)	− 0.14 (0.058)	− 0.37 (0.073)§	− 1.11 (0.197)§**	<.001

* E_4- includes $E_{2/2}$, $E_{2/3}$, $E_{3/3}$; E_4 heterozygotes include $E_{4/3}$, $E_{4/2}$; E_4 homozygotes are $E_{4/4}$. The number of subjects given is the maximum in each group. Data are adjusted for age, sex, country, education, history of vascular disease, history of myocardial infarction, history of diabetes mellitus, history of stroke or transient ischemic attack, smoking, use of antihypertensive medication, blood pressure, body mass index, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglyceride, and where applicable test version. Change score (last recorded result minus baseline result) was also adjusted for baseline test score and baseline test score and treatment allocation.

† *P*-value for test of heterogeneity across groups.

‡ Note a positive change in the Stroop test indicates a deteriorating performance.

§ E_4 heterozygotes or E_4 homozygotes differ significantly from E_4-.

** E_4 homozygotes differ significantly from E_4 heterozygotes.

Barthel or IADL indices. MMSE scores of E_4 homozygotes were significantly lower than those with E_4- ($P=.004$), but the comparison between the former and E_4 heterozygotes was not significant ($P=.11$), although the means differed. Memory tests exhibited a trend toward stepwise reduction with E_4 gene dosage. E_4 homozygotes and heterozygotes had significantly lower scores than E_4-, although possibly because of small subgroup size, the mean scores of homozygotes while tending to be lower than those of heterozygotes, were not significantly different ($P=.17$ for immediate memory; $P=.07$ for delayed memory).

The decline in performance on the Stroop and Letter-Digit Coding tests was not significantly different in E_4-, E_4 heterozygotes, and E_4 homozygotes (Table 3). For the immediate and delayed memory tests, the decrement in mean score for the E_4 homozygotes was significantly greater than that for the heterozygotes ($P=.006$ for immediate; $P<.001$ for delayed memory). In turn, the decline for E_4 heterozygotes was greater than that for E_4- ($P=.001$ for immediate memory; $P=.004$ for delayed memory). A similar pattern was present for change in MMSE ($P<.001$ for E_4 homozygotes vs heterozygotes; $P<.001$ for heterozygotes vs E_4-). To test the effect of baseline MMSE score on the association between apolipoprotein E phenotype and decline in memory function, an average percentage decline in the scores for the immediate and delayed Picture-Word recall was computed. This combined variable gave significant differences for E_4 homozygotes, E_4 heterozygotes, and E_4- subjects in the whole cohort (Figure 1) and the apolipoprotein E effect persisted when subjects were restricted to those with MMSE scores of 26 to 30. A similar pattern was seen in subjects with baseline MMSE scores of 28 to 30, with an overall significant effect of phenotype; intergroup comparisons were at the border of significance, probably because of smaller numbers of patients.

Influence of Lipoprotein Levels

Examination of the association between lipoprotein plasma levels and cognitive function at baseline revealed generally weaker relationships than seen with apolipoprotein E_4 status (Table 4). Results of the Picture-Word Recall tests were similar in all tertiles of LDL-C and HDL-C. The Letter-Digit test was significantly related to LDL-C, with poorer

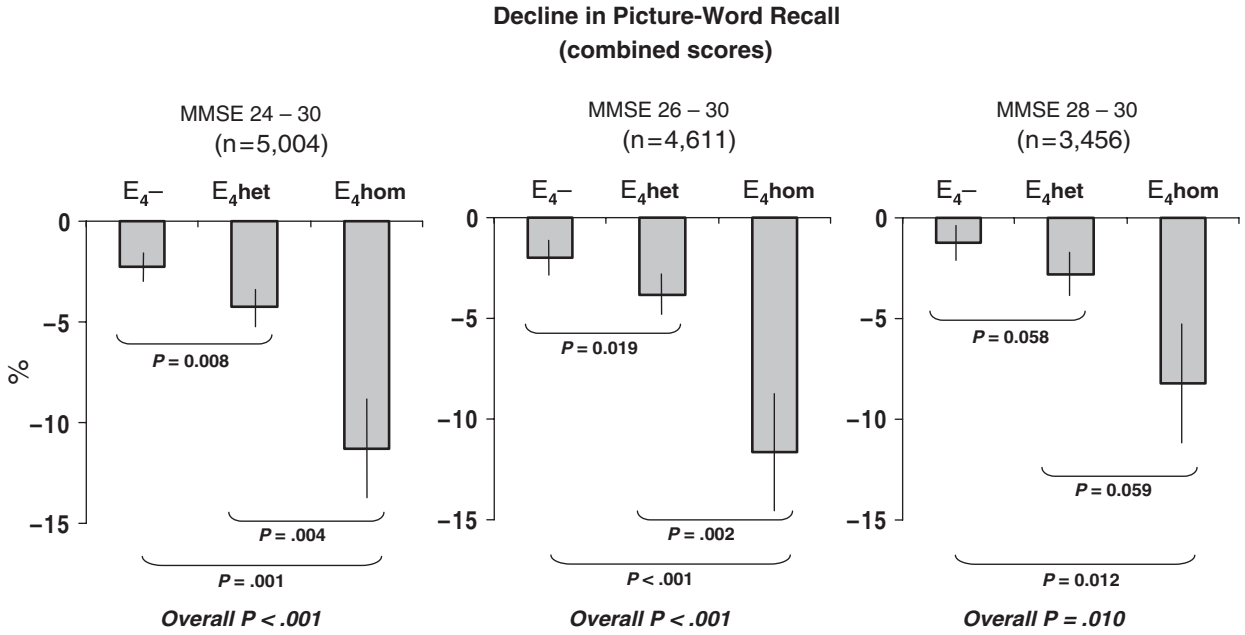

Figure 1. Decline in memory performance in apolipoprotein E_4 homozygotes, E_4 heterozygotes, and those without E_4. An average percentage change was calculated from the results of the immediate and delayed Picture-Word Recall scores. The influence of apolipoprotein E_4 status on this variable was examined in subjects with differing Mini-Mental State Examination (MMSE) score ranges at baseline. Least square mean changes (with standard errors) are given for E_4- subjects, E_4 heterozygotes (E_4 het), and E_4 homozygotes (E_4 hom). These were adjusted for the factors listed in the footnote to Table 1 and for treatment allocation. Significance levels are given for an overall effect and for intergroup comparisons. The number of evaluable subjects within a specific baseline MMSE range is provided (i.e., those with apolipoprotein E analysis and follow-up cognitive function scores available).

scores being seen in the lowest LDL-C tertile, and the Stroop test showed a trend in the same direction. The Barthel and IADL indices were significantly related to LDL-C level, with lower scores again being seen in the lowest tertiles. No significant association was observed between these indices and HDL-C.

Lipoprotein concentrations at baseline had no significant effect on change in cognitive function or decrease in score on the MMSE or the Barthel or IADL index (Table 4).

DISCUSSION

This study of the determinants of cognition in elderly adults found a marked effect of apolipoprotein E phenotype on memory performance that was apparent in the cross-sectional comparison at baseline and in the change over an average of 3.2 years of follow-up. Greater decline in memory in those with apolipoprotein E_4 occurred irrespective of baseline levels of global cognitive function (as assessed by MMSE). This suggested that the phenotype has a general population effect, not just an influence in those with signs of impaired cognition. Furthermore, the association between apolipoprotein E_4 and greater decline on the IADL index indicates that, at a population level, this phenotype has clinically important effects even in those who do not exhibit frank dementia. In contrast to the changes in memory performance, over this time scale, this genetic variation affected tests of the attention and processing cognitive domain to a much lesser extent. Plasma lipoprotein levels had limited influence on cognition at baseline and on its decline during follow-up.

After the initial reports of an association between Alzheimer's disease and apolipoprotein E phenotype,[7] it has been demonstrated repeatedly that subjects possessing apolipoprotein E_4, particularly homozygotes, have a high risk of developing dementia.[10–15] The underlying mechanism is thought in part to be more beta-amyloid deposits in the presence of E_4 than with other isoforms of the apolipoprotein,[8,43] although it is increasingly clear that apolipoprotein E phenotype has multiple effects on neurobiology.[21] Alzheimer's disease, characterized by episodic memory loss, is likely to be the end result of a long subclinical degenerative process, and the question arises as to when and how apolipoprotein E_4 contributes to this less-obvious pathology. As has been noted,[11,13] early studies of the influence of apolipoprotein E_4 on the rate of cognitive decline in the apparently normal population involved small numbers of subjects and included those with frank dementia or cognitive impairment at baseline or during subsequent evaluations. For example, one study[44] reported a greater decrease in MMSE score and in information processing speed in elderly subjects with no initial cognitive impairment who were apolipoprotein E_4 carriers; results for memory function were less clearcut, showing no significant drop. In that study, there was a fall of 0.8 to 1.4 points in the MMSE score, indicating that a number of subjects developed significant cognitive impairment during the assessment period. In the Cognitive Function and Ageing Study, apolipoprotein E phenotype was linked to risk of dementia (as determined according to MMSE score) in the cross-sectional survey, but no association was seen with incident dementia over 6 years.[45] Results supporting a link between apolipoprotein E_4 and memory impairment came from a study of 611

Table 4. Comparison of Baseline Measures of Cognition and Cognitive Decline According to Tertile of Low-Density Lipoprotein Cholesterol (LDL-C) and High-Density Lipoprotein Cholesterol (HDL-C)

		LDL-C†				HDL-C†			
Cognitive Test*	Tertile	Baseline Mean (SE)‡	*P*-Value§	Change Mean (SE)‡	*P*-Value§	Baseline Mean (SE)‡	*P*-Value§	Change Mean (SE)‡	*P*-Value§
Stroop Part III (seconds to complete)	I	71.1 (0.88)	.07	+5.08 (0.80)	.21	69.4 (0.90)	.07	+6.23 (0.82)	.36
	II	68.8 (0.89)		+5.09 (0.81)		71.1 (0.91)		+5.28 (0.83)	
	III	69.0 (0.91)		+6.37 (0.83)		68.9 (0.93)		+4.92 (0.84)	
Letter-Digit Coding (number correct)	I	22.0 (0.24)	.01	− 1.71 (0.16)	.33	22.4 (0.25)	.92	− 1.75 (0.17)	.55
	II	22.4 (0.24)		− 1.75 (0.16)		22.0 (0.25)		− 1.73 (0.17)	
	III	22.5 (0.25)		− 1.79 (0.17)		22.5 (0.26)		− 1.76 (0.17)	
Picture-Word Recall—immediate (number recalled)	I	9.21 (0.065)	.25	− 0.44 (0.064)	.53	9.22 (0.066)	.88	− 0.35 (0.065)	.17
	II	.30 (0.065)		− 0.36 (0.064)		9.29 (0.068)		0.45 (0.067)	
	III	9.27 (0.065)		− 0.44 (0.066)		9.29 (0.068)		− 0.44 (0.068)	
Picture-Word Recall—delayed (number recalled)	I	9.93 (0.092)	1.00	− 0.74 (0.092)	.75	9.90 (0.094)	.62	− 0.62 (0.094)	.16
	II	9.94 (0.093)		− 0.54 (0.093)		10.01 (0.096)		− 0.64 (0.096)	
	III	9.93 (0.096)		− 0.73 (0.095)		9.93 (0.097)		− 0.74 (0.097)	
Barthel Index (score)	I	19.57 (0.026)	.001	− 0.61 (0.065)	.59	19.59 (0.026)	.08	− 0.58 (0.066)	.34
	II	19.65 (0.026)		− 0.52 (0.061)		19.62 (0.026)		− 0.56 (0.067)	
	III	19.67 (0.026)		− 0.58 (0.067)		19.68 (0.027)		− 0.57 (0.068)	
Instrumental activity of daily living index (score)	I	13.35 (0.035)	.01	− 1.06 (0.078)	.96	13.38 (0.034)	.06	− 1.08 (0.079)	.23
	II	13.46 (0.035)		− 1.01 (0.078)		13.41 (0.037)		− 0.97 (0.081)	
	III	13.45 (0.036)		− 1.06 (0.080)		13.46 (0.037)		− 1.06 (0.082)	
Mini-Mental State Examination (score)	I	27.9 (0.054)	.51	− 0.30 (0.068)	.61	27.9 (0.055)	.72	− 0.28 (0.070)	.82
	II	27.9 (0.054)		− 0.25 (0.068)		27.9 (0.056)		− 0.28 (0.071)	
	III	27.9 (0.055)		− 0.30 (0.071)		27.9 (0.056)		− 0.28 (0.072)	

* The numbers for each test are shown in Table 1 for baseline models and Table 2 for change models.

† Tertiles of LDL-C were I <3.40, II 3.40–4.10, III >4.10 mmol/L, tertiles of HDL-C were I <1.10, II 1.10–1.37, III >1.37 mmol/L.

§ *P*-value for continuous measure of HDL-C or LDL-C (as appropriate).

‡ Least squares mean (standard error) for baseline result or for change (last recorded results minus baseline result) score adjusted for age, sex, country, education, history of vascular disease, history of myocardial infarction, history of stroke or transient ischemic attack, smoking, use of antihypertensive medication, blood pressure, body mass index, HDL-C or LDL-C (i.e., HDL-C was included in the model when LDL-C levels were tested and vice versa), plasma triglyceride, apolipoprotein E_4, and where applicable test version. Change was also adjusted for baseline test score and treatment allocation.

elderly clergymen, in which it was seen that E_4 had a more-pronounced influence on the decline in episodic memory than on other cognitive domains.[46] Again, the 16.7% incidence of clinically evident Alzheimer's disease may have influenced the result. More recently, in a report on the long-term follow-up of cognitive function in subjects aged 70 to 79 who were free of obvious dementia at baseline, apolipoprotein E_4 was associated at 7 years but not at 3 years of follow-up with reduced memory function and decreased ability in other cognitive areas.[47] Furthermore, in 840 cognitively normal elderly subjects followed for 3.5 years, apolipoprotein E phenotype and depression contributed to the appearance of mild cognitive impairment, apparently in an additive fashion.[6] In contrast, in a population-based study[13] in which subjects with dementia at baseline and at various stages of follow-up were excluded from the analysis, a greater preclinical decline in MMSE was present in participants who went on to develop dementia, but apolipoprotein E status had no influence on this change or on the rate of cognitive decline in those who were free of dementia throughout. Thus, debate continues about the influence of apolipoprotein E on cognition in the healthy aging population without dementia.

The present study has a number of features that should be borne in mind in assessing its conclusions. It followed a large cohort, and the majority of subjects had good cognitive function at baseline. Because of short follow-up, few developed dementia or poor general cognitive function. (Mean decrease in MMSE score was 0.13, and 89.3% of E_4+ and 92.8% of E_4 − subjects had MMSE scores >24 at their final assessment.) Dementia was not a formal study-specific diagnosis but was recorded as an adverse event. On entry, subjects were selected to have a history of, or to be at risk of, a vascular event, and the results should be extrapolated to the general public in light of this design feature. In addition, half of the subjects were allocated to receive pravastatin, but the drug had no discernible effect on cognitive decline, and it is likely that treatment did not confound the result.[27]

Overall, a consistent influence of apolipoprotein E_4 on memory function in the immediate and delayed recall tests was observed at baseline and during follow-up. This contrasted with the relative lack of influence of E_4 on attention and processing (assessed by the Letter-Digit Coding test at baseline and follow-up and the Stroop test at follow-up). Furthermore, there was evidence of a gene dosage effect, with E_4 homozygotes faring worse than heterozygotes. These results echo the findings of a meta-analysis of cross-sectional studies by,[11] which concluded that, in the general aging population, the influence of apolipoprotein E genotype is small in magnitude and specific to certain domains of cognitive function. The findings of the current study, together with other,[11,15] but not all,[13,20] comparable observations, raise the possibility that apolipoprotein E_4 is a determinant of the trajectory of memory loss (and consequent cognitive decline) in the elderly general population.

Vascular dementia and Alzheimer's disease have a considerable degree of overlap in terms of neuropsychological impairments, although there is a tendency for vascular dementia to be associated with greater deficits in attention, speed of information processing, and executive function,[48] whereas subjects with Alzheimer's disease have more problems with semantic memory.[49,50] Thus, it was of interest to evaluate whether plasma lipoproteins potentially linked to vascular disease influenced specific domains of cognitive impairment. It was found that associations between lipoprotein levels and cognitive function tests were of borderline significance or not significant at baseline and during follow-up. The most notable observation was that low LDL-C levels independent of vascular disease history were associated with marginally poorer ADL and IADL scores; HDL-C exhibited a similar trend. Analogous findings were reported in the Leiden 85 Plus study,[23] with low HDL-C being linked to poorer MMSE scores in subjects with and without a history of cardiovascular disease, although in that study, LDL-C showed no association with cognition. One possible explanation for the findings of the current study is that less-able elderly people are nutritionally compromised, and this leads to both lipoproteins being reduced, although a direct influence of lipoproteins on some cognitive aspects of disability cannot be excluded. Similar results were reported recently in a study that found no association between cholesterol or HDL-C and risk of dementia in a community-based study of cognitively intact elderly subjects.[26]

In conclusion, this large-scale cognition study embedded in a clinical trial revealed that, over an average 3.2-year period, the presence of the apolipoprotein E_4 isoform was associated with greater decline in memory performance without apparently affecting attention or processing ability. The apolipoprotein E4 isoform was linked also to more-pronounced deterioration in indices of ADLs and IADLs.

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